Before the
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

In re: International Drug Scheduling;	)	
Convention on Psychotropic Substances;	)	
Single convention on Narcotic Drugs;	)	**Docket No. 98N-0148**
World Health Organization Scheduling	)	
Recommendations for Ephedrine,	)	
Dihydroetorphine, Remifentanil, and	)	
Certain Isomers	)	

COMMENTS OF WEIDER NUTRITION INTERNATIONAL, INC.

Weider Nutrition International, Inc. ("Weider"), by counsel and in response to the Notice, 64 Fed. Reg. 1629 (Jan. 11, 1999), in the above-referenced proceeding, hereby submits these comments on the recommendations by the World Health Organization (WHO). WHO recommends that member states agree to impose licensing and import and export restrictions on manufacturers and distributors of ephedrine and for member states to mete out penalties for noncompliance. For the foregoing reasons, Weider opposes the promulgation of the proposed international law. Weider favors instead (in light of accepted, widely varying food and medicinal uses of ephedrine-containing products worldwide) that the 12 member states that have experienced ephedrine abuse develop their own domestic regulatory schemes to combat that abuse. Because of wide variance in accepted uses from nation to nation, the WHO recommendations for one international law and standard threatens to limit and prevent traditional, common and accepted uses of ephedrine within individual member states, to the detriment of public health and convenience. To avoid the imposition of international restrictions that could produce detrimental health effects by limiting or preventing accepted uses, the United States should oppose the WHO recommendations. It should instead encourage each of

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the 12 member states reporting abuse to adopt regulations of their own, as necessary to counter domestic abuse.

I. BACKGROUND OF COMMENTER

A Utah corporation, Weider is one of the largest suppliers of health, fitness, and wellness products worldwide. Weider manufactures and markets products in the sports nutrition, bottled drink, diet, natural vitamin, and nutritionally based snack bar categories, including some supplements that contain ephedrine alkaloids. Weider has been a health, fitness and sports nutrition leader for sixty years since its founding in 1939.

II. SUMMARY OF WHO RECOMMENDATIONS TO CONTROL EPHEDRINE AND OTHER SUBSTANCES UNDER INTERNATIONAL DRUG CONTROL TREATIES

In its Notification on l-ephedrine and d.l-ephedrine, WHO urges member nations to agree to international regulation of the import and export, and of the domestic manufacture, sale and distribution, of l-ephedrine and d.l-ephedrine. WHO acts pursuant to article 2, paragraphs 1 and 4, of the Convention on Psychotropic Substances of 1971 (Convention) to which the United States is a party. WHO seeks to place 2-methylamino-l-phenylpropan-1-ol (l-ephedrine) and racemate 2-methylamino-l-phenylpropan-1-ol (d.l-ephedrine) in Schedule IV of the Convention.

WHO describes ephedrine as an amphetamine-like substance (less potent to the central nervous system than amphetamines but more effective as a bronchodilator). Ephedrine is said to increase motor activity and mental alertness and diminish fatigue. It is also said to decrease appetite and promote weight loss. 64 Fed. Reg. at 1630. A bronchodilator in the symptomatic treatment of reversible bronchospasm, ephedrine is described as useful in the treatment of asthma, bronchitis, emphysema, and other obstructive pulmonary

diseases. Ephedrine is also reported to be used in the treatment of hypotension and shock, obesity, motion sickness, and enuresis. Id.

In the WHO Ephedrine Report (Annex 2 to its Notice), WHO recounts that it sent surveys to 191 countries, receiving only 50 responses. Of the 50 responses, a total of 46 reported ephedrine available for medical use. Of the 46, only 12 reported present or past instances of abuse or illicit trafficking in ephedrine: Belgium, Burkina Faso, China, Costa Rica, Germany, Finland, France, Ireland, Sudan, Slovakia, Thailand, and the United States. The reported instances of abuse vary greatly from country to country. Indeed of the twelve, Belgium reports no need for controls in light of only "sporadic reports" of abuse. Burkina Faso reports no information on abuse, yet it is listed among the twelve apparently because it reported smuggling from neighboring countries. China, German, and the Sudan report that abuse no longer occurs due to domestic controls. Finland, France, and Ireland report only a few cases of abuse. Of the twelve, only three (Sweden, Thailand, and the United States) report more than a few cases of abuse. The 12 reporting countries provided WHO with the following responses, summarized in Annex 2:

> BEL: Sporadic reports on ephedrine abuse. The view of the competent authority is that this level of abuse does not justify controlling ephedrine as a narcotic or psychotropic drug.
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> BFA: Three preparations are available on prescription. Though no information is provided on ephedrine abuse, BFA reported seizures of ephedrine tablets smuggled from neighbouring [sic] countries.
>
> CHN: Oral dosage forms are available. Ephedrine was abused in the past and resulting health problems stopped after it was placed under national control as a psychotropic drug.
>
> COR: Ephedrine abused as a doping agent.

DEU: 16 preparations are registered, some as prescription drugs and others are OTCs. Abused by drug addicts in the past, which decreased after withdrawal of many of the preparations from the market.

FIN: Available on prescription. Some misuse exists, as indicated by a few abusers visiting treatment centres. A few cases of diversion on falsified prescriptions and illegal importations were discovered.

FRA: 24 preparations of different dosage forms are available, of which 18 are OTC. A few cases of ephedrine abuse are reported in the capital region. Though a significant increase in seizures of ephedrine was reported, there was no clear indication of the purpose of use.

IRE: Tablets are available on prescription. Seized MDMA samples were found to contain ephedrine, suggesting some abuse as a substitute for MDMA.

SUD: Ephedrine importation was stopped because of its abuse as a stimulant.

SVK: Seven preparations of different dosage forms are sold. A few cases of misuse, and significant amounts of seizures in connection with clandestine manufacturing of stimulants.

THA: Approximately 40 kg/year is used as a nasal decongestant. A few cases of abuse are known to the police, as well as illicit trafficking as a precursor in border areas.

USA: Ephedrine is sold as a single entity or in combination with multiple ingredients, both as a prescription and OTC medication. In addition, Ma Huang and extracts are sold as dietary supplements. DAWN data indicate an increase in drug abuse episodes of ephedrine and pseudoephedrine. Subsequent analyses indicated that the incidence with pseudoephedrine was higher than for ephedrine. STRIDE data for the 6-year period 1992-1997 indicated about 700 exhibits involving small quantities (200 tablets or less) of ephedrine, representing about 300 cases, were likely to have been associated with ephedrine abuse. Adverse events tabulated for ephedrine products sold as food supplements for the State of Texas were reported by the Centers for Disease Control (CDC).

Annex 2 at 8-9.

WHO justifies its recommendations for international restriction of ephedrine on the foregoing relatively scant evidence of global abuse, and not on instances of accepted

use, including medicinal use (represented to involve 46 member states). Ephedrine is thus challenged not on the argument that it is intrinsically harmful but on the argument that it may be abused and has been in a minority of member states. Moreover, WHO recommends that only the l-isomer be controlled, not the d-isomer. Furthermore, it finds that combination ephedrine products would be eligible for exemption according to the 1971 Convention. WHO reports that effective international regulation of ephedrine will be difficult because further clarification is needed by member states due to overlapping jurisdictions concerning the 1971 Convention and the 1988 UN Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances.

Under the 1971 Convention, when a substance is added to Schedule IV, member states are (1) to require licenses for manufacture, trade and distribution in accordance with Article 8 of the Convention; (2) to comply with the obligations of Article 13 of the Convention regarding prohibition of and restrictions on export and import; and (3) to adopt measures in accordance with Article 22 for the repression of acts contrary to the laws or regulations adopted. Under Article 13, country-wide prohibitions on imports may be enforced against other member states that have allowed export of the Schedule IV substances. Under Article 22, member states are encouraged to impose punishments under their domestic laws against violators and to extradite persons for trial and punishment to other member states where violations have taken place.

Thus, the WHO recommendations essentially call for the development of new and far-reaching international trade restrictions on the manufacture, sale, and distribution of ephedrine-containing products. They thus create governance independent of national laws and, by affecting domestic trade, provide for a general restriction on the distribution

of the Schedule IV substances within all member states, not just the 12 that reported instances of present or past abuse or illicit trafficking.

III. SUMMARY OF CURRENT U.S. POSITION ON EPHEDRINE-CONTAINING PRODUCTS

In the United States ephedrine-containing products are foods, dietary supplements, or drugs depending upon their labeling. Products represented on their labels or in their labeling for use in the diagnosis, cure, mitigation, treatment, or prevention of disease are drugs. 21 U.S.C. § 321(g)(1)(B). Those labeled as dietary supplements without disease claims are regulated as dietary supplements if, like ephedrine, they are extracts of botanicals (among other categories). 21 U.S.C. § 321(ff). Ephedrine contained in foods in common form (not represented for use in the diagnosis, cure, mitigation, treatment, or prevention of disease) are considered foods. 21 U.S.C. § 321(f). On June 4, 1997, the FDA published a proposed rule in the Federal Register, proposing to regulate the presence of and dosage and warning labels for ephedrine-containing dietary supplements. 62 Fed. Reg. 30678. The agency has not yet promulgated a final rule.

IV. SUMMARY OF WEIDER'S OPPOSITION TO WHO RECOMMENDATIONS

Weider opposes the imposition of any international restrictions on the import, export, manufacture, sale, and distribution of ephedrine-containing products. Weider opposes the WHO recommendations for the following reasons, explained in greater detail below. (1) WHO's proposal is incongruous and the means chosen are unlikely to further the ends desired; rather the means (general restrictions) are likely to deprive those in need

of accepted uses from access to ephedrine-containing products. WHO would impose global restrictions on ephedrine-containing products (thus denying access to those who seek the product for accepted uses) in order to further the interest of stemming abuse, yet instances of abuse may occur nonetheless either through continued illicit international trafficking or through domestic abuse of approved national sources of ephedrine. (2) In the absence of congressional legislation authorizing restriction on the manufacture, sale, and distribution of the dietary supplement ephedrine, any unilateral action by the Food and Drug Administration to encourage that result violates the Dietary Supplement Health and Education Act of 1994, which is designed in principal part to ensure that no restrictions are placed upon accepted uses of dietary supplements (including those containing ephedrine). Thus, while adulterated products may lawfully be enjoined from being sold consistent with the FDCA, 21 U.S.C. § 342, dietary supplement products that are not adulterated—such as those involving accepted uses of ephedrine listed in the UN notice—are fully protected from restriction by the DSHEA. (3) No evidence exists to establish that the 12 reporting states have been unable or are unwilling to combat instances of domestic abuse through the use of national and local law enforcement. To justify the imposition of an international regulation on all member states, evidence is needed of general harm affecting the vast majority of member states and of the insufficiency of domestic laws to combat the abuse. That evidence does not exist. (4) Ephedrine assumes various forms (foods, dietary supplements, and drugs) throughout the world and accepted uses vary greatly. The diversity of the substance and the diversity of its accepted uses militate against uniform international regulation which could interfere with national laws, policies, customs, and accepted uses. (5) Member states' regulations

of the product vary greatly. Matters of health regulation are necessarily local concerns that—in the absence of international abuse affecting all member states—are best left to local authorities.

V. ARGUMENT

A. THE U.S. SHOULD OPPOSE ADOPTION OF THE WHO RECOMMENDATIONS

1. The WHO Recommendations on Ephedrine-Containing Products Are Not Narrowly Tailored to Achieve WHO's Desired Ends; Rather, They Threaten to Limit or Eliminate Accepted Uses of Ephedrine-Containing Products

WHO recognizes that ephedrine-containing products have accepted uses. Among those it lists in its notice are treatments for asthma, bronchitis, emphysema, other obstructive pulmonary diseases, shock, obesity, motion sickness, and enuresis. In addition to those listed by WHO, ephedra (including its constituents in the ephedrine family) are used as foods.[1] WHO reports that the only reports of ephedrine abuse come from 12 member states out of 49 responding. The specific kinds of abuses occurring in those member states vary greatly based on the unique local cultures in those countries and historic domestic patterns of food, drug, and dietary supplement use and abuse. The

[1] The 40 species of ephedra can be found in all four of the southwestern deserts of the United States. It is indigenous to northwest India, Pakistan, and China. Ephedra has been used for thousands of years, primarily in China and India, and has a history of safe use there and in North American when consumed in moderation as foods, dietary supplements, or medicinal herbs. The use of ephedrine, or ma-huang, has been traced as far back as 3000 B.C. In ancient China it was used as a medicinal agent by Chinese physicians who prescribed it for various respiratory conditions such as colds, asthma and hay fever. Michael Stuart, The Encyclopedia of Herbs and Herbalism (1979). Ephedrine has also been traditionally used in the United States. Ephedra is cultivated in the dry regions of North America and is consumed as "Mormon Tea" or "Squaw Tea." In 1847 when the Mormons arrived in Utah, the native Indians introduced them to ephedrine. The Mormons used it as a substitute for coffee and black tea and to treat medical conditions such as asthma and hay fever. Ephedrine was also used to make bread. The history reflects no safety problems arising from consumption of ephedrine in teas and foods. Jane Rose, Herbs and Things (1972).

definition of what constitutes abuse varies greatly such that accepted uses in one country are viewed as abuse in another.

Despite the fact that only 12 member states report abuses of, or illicit trafficking in, ephedrine-containing products, WHO recommends adoption of a general international regulation that would restrict manufacture, sale, and distribution along with import and export of ephedrine-containing products worldwide. Despite the fact that WHO recognizes the existence of many accepted uses of ephedrine-containing products, WHO recommends adoption of a general international regulation that would harm accepted uses by making it more difficult to manufacture, sell, and distribute and to import and export ephedrine-containing products. At a minimum effective enforcement of restrictions will increase the costs of those products, placing them beyond the reach of the poor who may depend upon them the most in the treatment of chronic respiratory conditions and obesity.

Because of the limited number of states that have reported abuses (only Sweden, Thailand, and the United States report more than a few cases), the fact that ephedrine-containing products do have accepted uses, and the fact that restrictions on manufacture, sale, distribution, import, and export will limit the availability of those products to those in need, the United States should oppose adoption of the WHO recommendations.

2. The United States Is Legally Barred from Supporting International Restrictions on Manufacture, Sale, Distribution, Import, and Export of Ephedrine-Containing Products

Congress has not authorized FDA to restrict the manufacture, sale, distribution, import, or export of dietary supplements, including those containing ephedrine. To the contrary, any unilateral action by FDA to encourage that result in the absence of specific proof of adulteration in an individual case violates the FDCA as amended. In particular,

the FDCA places the burden on the agency to prove that a particular dietary supplement is adulterated before it may remove the product from the market. 21 U.S.C. § 342. FDA may not—consistent with its statutory mandate—favor the adoption of an international regulation that would conflict with its duty to protect safe and accepted uses of ephedrine-containing products and to prove adulteration case-by-case, rather than by the imposition of general restrictions on manufacture, sale, distribution, import, and export of all ephedrine-containing products. It is axiomatic that FDA is a creature of Congress and may not extend its jurisdiction beyond that statutorily granted to the agency. Congress has not seen fit to allow FDA to do internationally that which it is prohibited from doing domestically. Consequently, FDA is legally barred from supporting the WHO recommendations.

3. No Evidence Exists to Prove that the 12 Member States Reporting Domestic Abuses Are Either Unable or Unwilling to Combat That Abuse Through the Use of National and Local Law Enforcement

To justify the imposition of an international regulation affecting all member states, evidence is needed of general harm affecting the vast majority and of the insufficiency of domestic laws to combat that abuse. That evidence is lacking. Only 12 of 46 member states reported abuse or illicit trafficking. None of the 12 has reported an inability to combat that abuse or trafficking through the use of domestic laws, and no general proof exists of a pervasive, international problem at this point. As a consequence, the recommendation for adoption of international law is premature. The risks associated with adopting international restrictions prematurely are palpable. In this instance, they threaten to cause economic injury to member states whose domestic manufactures include companies that make ephedrine-containing products for accepted

uses. Moreover, they threaten to obstruct consumer access for accepted uses and thereby harm consumers through increased costs or through denial of needed treatments. Consequently, FDA should oppose the adoption of the WHO recommendations and encourage instead that each of the 12 member states experiencing abuse rely upon domestic laws to combat those abuses.

4. Ephedrine Assumes Various Forms (Foods, Dietary Supplements, and Drugs) and Accepted Uses Vary, Militating Against a One-Size-Fits All International Regulatory Regime

Ephedra has been used in different cultures in different ways: as a healing herb, as a food ingredient, as a food, as a tea, and as a beverage. As a healing herb, ephedra serves as a nasal decongestant, a central nervous system stimulant, and a treatment for bronchial asthma. Varro E. Tyler, The Honest Herbal – A Sensible Guide to the Use of Herbs and Related Remedies (1993); M. B. Krieg, Green Medicine (1964).

While ephedra is widely used as a healing herb, it is also considered a food in several regions of the world. For example in India the berry from the ephedra shrub is consumed as a fruit. Also certain tribes from the Himalayas use the ephedra berry as a food source. Among desert plants, the ephedra species is extremely high in Vitamin C which makes it a major contributor to vitamin requirements of humans subsisting on the local food-flora. S.A. Grebinski and B.I. Yaroshkin, Vitamin C in Desert Plants (1953).

Each country has its own unique pattern of ephedrine use and abuse. Each country has its own unique safety record. Each country's people have their own peculiar reliance upon ephedrine. In some countries ephedrine (the berry from the ephedra shrub) is a food source important to human survival and welfare. In other countries it is an important food additive in baked goods, including breads. In other countries it is

consumed as a tea or other beverage. In still others, it is available as a dietary supplement, herbal remedy, OTC drug, or prescription drug. Relied upon for widely varying purposes that range from sustenance to asthma treatment, ephedrine has great importance around the world. Uniform categorization of ephedrine as a controlled substance is, thus, inappropriate.

Any restriction such a classification would impose on an accepted national or local use within a member state could have profoundly adverse consequences. International regulation could deprive people in different societies of important food sources, nutritional supplements, herbal remedies, or prescription drugs. While WHO recites the existence of accepted uses known to it, WHO has not conducted any research on the impact its recommendation would have upon those accepted uses. At a minimum before recommending restrictions on manufacture, sale, distribution, import, and export of ephedrine-containing products, WHO should perform a thorough study of customary and accepted uses in each member state and ascertain how its recommendation, if adopted by member states, would affect those uses. It should then modify its recommendations to ensure that those customary and accepted uses are not adversely affected. WHO's recommendations could deprive people (particularly those least able to afford substitutes), including the large populations of poor who live in India, China, Africa, and Asia generally, of a needed herbal remedy. The United States should oppose adoption of the WHO recommendations until their impact is evaluated thoroughly and until they are tailored to avoid harm to accepted and customary uses of ephedrine.

5. Member States' Domestic Regulations of Ephedrine-Containing Products Vary Greatly and the WHO Recommendation Threatens the Unique Domestic Differences That Are Both Necessary and Sufficient to Combat Domestic Abuses

In case of ephedrine (a substance variously regulated as a food, a dietary supplement, and a drug in member states), each member state has responded differently to perceived instances of abuse. Those perceptions differ from member state to member state not only as to the gravity of the offense but also as to whether any particular use is deemed an offense. In Canada, ephedrine is regulated as a traditional herbal medicine (THM), while in England, ephedrine is sold by prescription only. In China, Japan and France, synthetic ephedrine products are regulated as OTCs. In Asian countries, naturally occurring ephedrine is available in herbal shops. Due to diverse uses and systems of regulation throughout the world, it would be inappropriate to regulate ephedrine under one uniform standard. Indeed, such a standard threatens to upset and replace national regulatory systems that are both necessary and sufficient to combat domestic abuses.

Each member state—faced with its own unique history of ephedrine use and abuse—is equipped with means both necessary and sufficient to address the specific problems encountered through domestic regulation. Domestic regulation is preferable to an international regime because it takes into account the unique social, cultural, historical use, and needs of each member state's people. Given the patchwork quilt of differing, sometimes conflicting, domestic policies and laws, one international restriction on manufacture, sale, distribution, import, and export of ephedrine-containing products will necessarily violate the needs and interests of some for whom domestic authorities have determined access is lawful, legitimate, and reasonable.

B. THE UNITED STATES SHOULD RECOMMEND THAT EACH MEMBER STATE DETERMINE HOW BEST TO REGULATE EPHEDRINE-CONTAINING PRODUCTS

In light of (1) the extraordinarily diverse uses of ephedrine (many of which WHO regards as accepted and legitimate), (2) the fact that the proposed recommendations would restrict even accepted and legitimate uses, (3) federal law preventing FDA from restricting the manufacture, sale, and distribution of dietary supplements absent proof of adulteration, (4) the fact that only a minority of member states report instances of domestic abuse, and (5) the absence of proof that the 12 member states reporting abuses are either unable or unwilling to combat domestic abuse with domestic laws, the United States should oppose the WHO recommendations to control ephedrine under the international drug control treaties. Such a move is not only legally required and appropriate for the reasons explained above, the WHO recommendations are premature in light of unresolved issues pertaining to overlapping jurisdictions concerning the 1971 Convention and the 1988 UN Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances.

VI. CONCLUSION

For the foregoing reasons, Weider Nutrition International, Inc. respectfully requests that the Food and Drug Administration oppose adoption of the WHO recommendations to control ephedrine through international regulation.

Respectfully submitted,
WEIDER NUTRITION
INTERNATIONAL, INC.

By: _____
Jonathan W. Emord
Andrea G. Ferrenz
Its Counsel

Emord & Associates, P.C.
1050 17th Street, N.W.
Suite 600
Washington, D.C. 20036
P: (202) 466-6937
F: (202) 466-6938

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